## Remarks

The Amendments

Claims 1-38 are canceled and replaced by new claims 39-97. Each of the new claims recites a particular amino acid or nucleotide sequence. The new claims are grouped for convenience according to claimed subject matter; for example, claims 39-49 recite a particular mammalian serine racemase comprising SEQ ID NO:8, isolated polynucleotides encoding the serine racemase, expression constructs comprising the polynucleotides, host cells comprising the expression constructs, and methods of producing the serine racemase.

Support for the new claims and their correspondence to subject matter of the canceled original claims are shown in the table below:

| **new claim** | **original claim** | **support** |
|---|---|---|
| 39 | 1, 7 | original claims 1, 7 |
| 40 | 14 | original claim 14; page 11, lines 25-26 |
| 41 | 14, 16 | original claims 14, 16 |
| 42 | 14, 21 | original claims 14, 21; page 14, lines 5-11; page 11, lines 25-29 |
| 43 | 14, 16, 21 | original claims 14, 16, and 21; page 14, lines 5-11; page 11, lines 25-29 |
| 44, 44 | 24 | original claim 24; page 14, lines 7-9, 18-19 |
| 46 | 24, 25 | original claims 24, 25; page 14, lines 7-9, 18-19 |
| 47, 48 | 24, 25, 28 | original claims 24, 25, 28; page 14, lines 7-9, 18-19 |
| 49 | 16, 24, 28 | original claims 16, 24, 28; page 14, lines 7-9, 18-19 |
| 50 | 1, 8 | original claims 1, 8 |
| 51 | 14 | original claim 14; page 11, lines 25-29 |
| 52 | 14, 19 | original claims 14, 19 |
| 53 | 14, 21 | original claim 21; page 14, lines 5-11; page 11, lines 25-29 |
| 54 | 14, 19, 22 | original claims 14, 19, 22 |

| | | |
|---|---|---|
| 55, 56 | 24 | original claim 24; page 14, lines 7-9, 18-19 |
| 57 | 24, 26 | original claims 24, 26; page 14, lines 7-9, 18-19 |
| 58, 59, 60 | 24, 26, 28 | original claims 24, 26, 28 |
| 61 | 32, 35 | original claims 32, 35 |
| 62 | 32, 33, 35 | original claims 32, 33, 35 |
| 63 | 32, 34, 35 | original claims 32, 34, 35 |
| 64 | 32, 37 | original claims 32, 37 |
| 65 | 32, 33, 37 | original claims 32, 33, 37 |
| 66 | 32, 24, 37 | original claims 32, 24, 37 |
| 67 | 1, 7, 8, 13 | original claims 1, 7, 8, 13 |
| 68 | 1, 4, 7, 13 | original claims 1, 4, 7, 13 |
| 69 | 1, 5, 7, 13 | original claims 1, 5, 7, 13 |
| 70 | 1, 6, 7, 13 | original claims 1, 6, 7, 13 |
| 71-76 | 13 | original claim 13; page 7, lines 4-7 |
| 77 | 1, 7, 8, 13, 14, 20 | original claims 1, 7, 8, 13, 14, 20; page 11, lines 25-29 |
| 78 | 1, 7, 13, 14, 20, 21 | original claims 1, 7, 13, 14, 20, 21; page 14, lines 5-11 |
| 79, 80 | 1, 7, 13, 14, 20, 24 | original claims 1, 7, 13, 14, 20, 24; page 14, lines 18-19 |
| 81, 82 | 1, 7, 13, 14, 24, 28 | original claims 1, 7, 13, 14, 24, 28 |
| 83 | 32, 34, 37 | original claim 32, 34, 37 |
| 84 | 32, 33, 37 | original claims 32, 33, 37 |
| 85 | 32, 34, 37 | original claims 32, 34, 37 |
| 86-92 | 20 | original claim 20; page 11, lines 25-29 |
| 93 | 20, 21 | original claims 20, 21; page 11, lines 25-29 |
| 94, 95 | 20, 21, 24 | original claims 20, 21, 24; page 11, lines 25-29 |
| 96, 97 | 20, 21, 24, 28 | original claims 20, 21, 24, 28; page 11, lines 25-29 |

The new claims do not add new matter.

Specification

As requested in the Office Action, an abstract is presented on a separate sheet. The abstract is supported by the abstract on the first page of the corresponding published PCT application and does not add new matter.

The Written Description Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6, 9-11, 12 (in part), 14, 15, 17, 18, 20 (in part), 21, 23 (in part), 24, 27 (in part), 28, 31 (in part), and 32-38 stand rejected under 35 U.S.C. § 112, first paragraph, as not sufficiently described in the specification. Claims 1-38 have been canceled. Applicants respectfully traverse the rejection with respect to new claims 39-97.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). Whether the specification meets the written

description requirement for the claimed invention is a question of fact. *Vas-Cath,* 935 F.2d at 1563, 19 U.S.P.Q.2d (BNA) at 1116.

The Office Action asserts that the functional features recited in originally filed claims 1-6, 9-11, 12 (in part), 14, 15, 17, 18, 20 (in part), 21, 23 (in part), 24, 27 (in part), 28, 31 (in part), and 32-38 were not sufficient to define structural features of species within the claimed genera. To advance prosecution, each of new claims 39-97 recites a specific amino acid or nucleotide sequence.

The Office Action acknowledges that the specification discloses serine racemases having the amino acid sequence of SEQ ID NO:8 and SEQ ID NO:10 and polynucleotides encoding these racemases. Office Action at paragraph bridging pages 3 and 4. The Office Action also acknowledges that the subject matter of original claims 7, 8, 16, 19, 22, 25, 26, 29, and 30, which recite SEQ ID NOS:8, 10, 1, or 9, is patentable. *Id.* at page 8. Thus, the rejection should not apply to new claims 39-66 because these claims are directed to the subject matter the Office Action acknowledges is patentable.

New claims 67-95 recite the following genera:

| claims | genera |
|---|---|
| 67-76, 83-85 | isolated mammalian serine racemases having a specific activity of at least 0.075 μmole L-serine/mg/hour and comprising an amino acid sequence that is at least 85% identical to SEQ ID NO:8 or SEQ ID NO:10; percent identity is determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1 |
| 77-82 | polynucleotides encoding mammalian serine racemases having a specific activity of at least 0.075 μmole L-serine/mg/hour and comprising an amino acid sequence that is at least 85% identical to SEQ ID NO:8 or SEQ ID NO:10; percent identity is determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1 |
| 86-97 | isolated polynucleotides that are at least 85% identical to the nucleotide sequence shown in SEQ ID NO:1 or SEQ ID NO:9 as determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1, wherein the polynucleotides encodes a mammalian serine racemase having a specific activity of at least 0.003 μmole L-serine/mg/hour |

The U.S. Patent and Trademark Office's Written Description Guidelines state that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . .

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal reference omitted, approved in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d (BNA) 1609, 1613 (Fed. Cir. 2002). The specification meets this standard for all three recited genera.

The specification teaches that "[s]erine racemase appears to be a very conserved enzyme." Page 5, lines 3. In light of this teaching, the specification discloses a sufficient number of species to describe the recited genera.

Each of the species within the genus of racemases recited in claims 67-76 and 83-85 has common structural features. Each of the recited serine racemases has the common structural feature of comprising an amino acid sequence that is at least 85% identical to either SEQ ID NO:8 or SEQ ID NO:10, where percent identity is determined using a specifically recited algorithm (Smith-Waterman) with particular, recited parameters (using an affine gap search with gap open penalty of 12, gap extension penalty of 1). The sequence properties are a structural feature. Each of the serine racemases within the recited genus also has the functional property of having a specific activity of at least 0.075 μmole L-serine/mg/hour. The specification discloses such serine racemases on page 5, lines 21-23.

Because of the well-known correlation between an amino acid sequence and the nucleotide sequences that can encode it (the genetic code), the specification also discloses to one skilled in the art this genus of polynucleotides. The genus of polynucleotides recited in claims 77-82 encode the serine racemases recited in claim 67 and discussed above. According to the genetic code there is a very precisely defined universe of nucleotide sequences that can encode any particular amino acid sequence. The known correlation between structure and the function of encoding is the well-known correlation between an amino acid and the three-nucleotide codons that encode that amino acid according to the genetic code: "For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be

unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence." Written Description Guidelines, 66 Fed. Reg. at 1111, n. 57.

Similarly, the specification also adequately describes the genus of polynucleotides recited in claims 86-97. The polynucleotides recited in claims 86-97 are at least 85% identical to SEQ ID NO:1 or SEQ ID NO:9 as determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1 and encode a functional mammalian serine racemase (*ie.*, having a specific activity of at least 0.003 μmole L-serine/mg/hour). Disclosure of SEQ ID NOS:1 and 9 together with the recited algorithm inherently describes all polynucleotides that are at least 85% (or 90, 95, 96, 97, 98, or 99%) identical to SEQ ID NOS:1 or 9.

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). The knowledge of one skilled in the art also must be considered, because the specification must "indicate[s] to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q.2d (BNA) 1945, 1948 (Fed. Cir. 2002). When read as a whole, taking into account the knowledge of persons skilled in the art at the January 19, 1999 priority date of the present application, this specification indicates to those skilled in the art that applicants invented the subject matter of claims 39-97 as of the application's filing date.

Applicants respectfully request withdrawal of the rejection.

The Enablement Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6, 9-11, 12 (in part), 13, 14, 15, 17, 18, 20, 21, 23, 24, 27, 28, and 31-38 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Claims 1-38 have been canceled. Applicants respectfully traverse the rejection with respect to new claims 39-97.

As an initial matter, the Office Action acknowledges that the specification enables serine racemases comprising the amino acid sequences of SEQ ID NO:8 and 10 and polynucleotides encoding SEQ ID NOS:8 and 10, including SEQ ID NOS:1 and 9. Office Action at page 5, second full paragraph. Thus, the rejection should not apply to new claims 39-66, each of which recites particular amino acid or nucleotide sequences.

The Office Action asserts that the specification does not enable a serine racemase of an undefined structure or polynucleotides encoding such a racemase. Office Action at page 5, second full paragraph. To advance prosecution, each of the new claims recites a specific amino acid sequence or nucleotide sequence.

The Office Action also asserts that the specification does not enable a serine racemase having an amino acid sequence 85% identical to SEQ ID NOS:8 or 10 or encoded by a polynucleotide 85% identical to SEQ ID NOS:1 or 9. Office Action at page 5, second full paragraph. First, the U.S. Patent and Trademark Office's concern that the skilled artisan would not be able to chose which amino acids to substitute does not apply to serine racemases isolated from mammals other than mouse or human. Such racemases can naturally contain amino acid substitutions with respect to SEQ ID NOS:8 or 10. The specification teaches how to isolate such serine racemases:

> Mammalian serine racemase can be isolated from homogenates of mammalian brain, such as rat, mouse, or preferably human brain.

> Other forms of mammalian serine racemase can be isolated from brain homogenates of other mammals, such as monkey, pig, cow, sheep, goat, guinea pig, and the like. The enzyme can be purified, partially or to homogeneity, using all or part of the method described in Example 1. This method employs, sequentially, ammonium sulfate fractionation, butyl-sepharose, Q-sepharose, mon-Q, and hydroxyapatite chromatography steps (Table 1).

Page 5, lines 14-20.

Second, the specification does in fact enable a serine racemase having an amino acid sequence 85% identical to SEQ ID NOS:8 or 10 or encoded by a polynucleotide 85% identical to SEQ ID NOS:1 or 9. The legal test for whether a disclosure provides adequate enablement for generic claims is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). The application meets this standard.

The specification discloses SEQ ID NOS:1, 8, 9, and 10. The specification discloses the Smith-Waterman algorithm recited in claims 66-97 and used to determine percent identity with the disclosed sequences. See page 7, lines 7-11, and page 11, lines 29-32. Claims 66-97 also recite the particular parameters to be used in the algorithm: "percent identity is determined according to the Smith-Waterman homology search algorithm, using an affine gap search with gap open penalty of 12 and a gap extension penalty of 1." See claims 66 and 86. The Smith-Waterman homology search algorithm was published in 1981, well before the January 19, 1999 priority date of the present application. Smith & Waterman, "Identification of Common Molecular Subsequences,"J Mol Biol. 1981 Mar 25;147(1):195-7. Thus, on the application's

priority date, those of skill in the art were familiar with using the algorithm to identify proteins having amino acid or polynucleotide sequences at least 85% identical to a reference sequence.

To support a finding of non-enablement, the U.S. Patent and Trademark Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d at 1562, 27 U.S.P.Q.2d (BNA) at 1513. The Office must not only explain why it doubts the statements in the specification's supporting disclosure, but also must support its assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). To support its assertion that serine racemase polypeptides that are at least 85% identical in amino acid sequence to SEQ ID NO:8 or 10 are not enabled, the Office Action asserts that

> the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting [sic; affecting] serine racemase activity; (B) the general tolerance of serine racemases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any serine racemase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Office Action at page 7, second full paragraph, emphasis in original. The specification, however, contains sufficient guidance to make the recited polypeptides.

Example 2 of the application teaches serine racemase assays. The specification also teaches the use of "routine protein analysis techniques." Page 6, lines 9-10. "These techniques include, but are not limited to, hydrophobicity and hydrophilicity plots, homology searches for various motifs, antigenic indices, and standard algorithms such as those disclosed in Harlow & Lane, ANTIBODIES – A LABORATORY MANUAL (Cold Spring Harbor Laboratory, 1988). Page 6,

lines 9-12. Carrying out such techniques, together with the serine racemase assays taught in Example 2, would guide one skilled in the art to which amino acids of SEQ ID NOS:8 or 10 could be altered while still retaining the specific activities recited in claims 67-76 and 83-85. Moreover, the specification teaches that mouse and human serine racemases contain a pyridoxal 5′ phosphate binding region (ELFQKTGSFKIRGA). See page 5, lines 30-31, SEQ ID NO:8 (amino acids 47-60), and SEQ ID NO:10 (amino acids 47-60). Because this binding region is conserved between the mouse and human serine racemases, one skilled in the art would realize its importance and be wary of making changes in this region.

Moreover, the choices for modification are not "essentially infinite," as asserted in the Office Action. If making amino acid substitutions in SEQ ID NOS:8 or 10, for example, one skilled in the art would tend to substitute amino acids with similar properties (*i.e.*, to make conservative amino acid substitutions). The universe of amino acids that can be substituted conservatively is well defined in the art (*e.g.*, Val↔Ile↔Leu, Asp↔Glu, Lys↔Arg, Asn↔Gln, and Phe↔Trp). *See* Alberts *et al.*, eds., MOLECULAR BIOLOGY OF THE CELL, 1983, pages 58-59 (attached). The U.S. Patent and Trademark Office's concern over this point is even less relevant with respect to dependent claims 71-76, which recite at least 90, 95, 96, 97, 98, or 99% identity with SEQ ID NO:8 or 10, respectively. A protein having at least 99% identity with SEQ ID NO:10, for example, would differ only in at most 3-4 amino acids (340 amino acids x 0.01).

The specification provides sufficient disclosure to enable one skilled in the art to make and use the polypeptides and polynucleotides recited in claims 66-97 without undue experimentation. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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